A

DISSERTATION ON

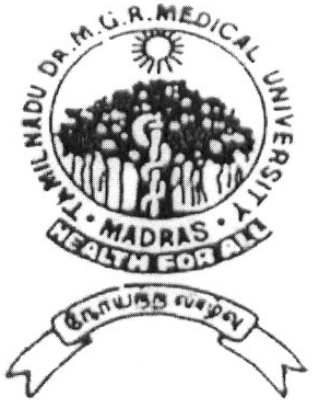
A STUDY OF RECURRENT STROKE

Submitted in partial fulfilment of
Requirements for the degree of

BRANCH - I D.M. (NEUROLOGY)

of

THE TAMILNADU Dr.M.G.R. MEDICAL UNIVERSITY
CHENNAI



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CERTIFICATE

This is to certify that this dissertation entitled "A study of Recurrent Stroke" submitted by Dr.P.V..KRISHNAN appearing for D.M. (NEUROLOGY) Degree examination in August 2008, is a bonafide record of work done by him under my direct guidance and supervision in partial fulfillment of regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai. I forward this to the Tamil Nadu Dr.M.G.R. Medical University, Chennai, Tamil Nadu, India.

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DECLARATION

I, **Dr.P.V.KRISHNAN** solemnly declare that the dissertation titled "A study of Recurrent Stroke" is done by me at Madras Medical College & Govt. General Hospital, Chennai during Jan.2006 – Dec.2007.

The dissertation is submitted to The Tamilnadu Dr.M.G.R. Medical University towards the partial fulfilment of requirements for the degree of D.M.(NEUROLOGY). I also declare that this dissertation have not formed the basis of the award of any degree or diploma of any university.

Place: Chennai
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Introduction

Stroke was defined according to the World Health Organization criteria as "rapidly developing symptoms and/or signs of focal, and at times global, loss of cerebral function, with symptoms lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin." The term "global" refers mainly to subarachnoid hemorrhage.

Recurrent stroke[1, 31] is defined as a stroke, in which (1) there was clinical evidence of the sudden onset of a new focal neurological deficit with no apparent cause other than that of vascular origin (ie, the deficit could not be ascribed to an intercurrent acute illness, epileptic seizure, or toxiceffect) occurring at any time after the index stroke; or (2) there was clinical evidence of the sudden onset of an exacerbation of a previous focal neurological deficit with no apparent cause other than that of vascular origin occurring 21 days after the index stroke.

Each recurrent stroke was classified as ischemic, hemorrhagic, or of undetermined nature on the basis of a CT or MRI scan performed within 28 days of recurrence or autopsy examination of the brain. Etiologic subtypes of ischemic stroke were defined according to Standardized criteria.

Conceptically the following definition is applicable in a community based

study .Recurrence represents the proportion of patients with stroke who had a second stroke during a specified period of observation. For example cumulative recurrence of stroke after surviving the first cerebral infarction in a population based study of Rochester ,Minnesota residents was approximately 6%.19%,29% at 1,5&10 years respectively.

If a stroke occurred during time interval 3-21 days, it often had to be in a different vascular territory or anatomical site from the first event, of a different stroke subtype, or result in a different neurological deficit, in order to be considered a recurrence.

A neurological worsening occurring at any time after the index event, following a period of stability of 24 h should be considered a potential recurrent stroke. This will not allow the very early recurrence risk to be underestimated.

Stroke-in-progression has been defined by the European Stroke Database collaboration as ‘neurological progression occurring within the first 3 days’.

There is a considerable variance of crude prevalence rates of cerebrovascular diseases across India. Vellore & Rohtak gave rates of 13& 33 per 100000 respectively(low) to 270 in Guwahathi, Assam. The crude

prevalence rate varied from 45-843 per 100000 with a high frequency of diabetes & poorly controlled. Hypertension patients with stroke are seen very frequently in daily Indian practice. Age adjusted mortality rates from stroke are considerably higher among Indians as against Europeans.

The immediate period after stroke comes the greatest risk for recurrence in stroke databank of 1273 patients with infarcty 3.3% had early recurrence within 30 days. Long term stroke recurrence range from 4% to 14% with aggregate annual estimate of 6.1% for minor and 9% for major stroke.

Based on WHO task force report on stroke prevention diagnosis and therapy-1989, it appeared that for large artery hypertension & smoking elevated blood lipid levels, obesity & diabetes are more important modifiable risk factors. Cardio embolic stroke, RHD&IHD seem to be the dominant risk factors among Indians. Broderick & Swanson of Rochester study reported a 1% annual stroke recurrence in patients with a mean follow up of 7 years(Broderick &Swanson 1987).This rate is significantly lower than the 9% reported by Rothrock In This study the incidence of recurrent stroke, various subtypes of presentation, etiologies, risk factors and the

effects of attempts at correction are analyzed.

The precise arterial pathology underlying lacunar infarcts, which are presumed to result from the occlusion of single, small perforating arteries, remains undetermined. It is often assumed to differ from the atherothromboembolic processes that occlude large intracranial and extracranial arteries and cause most other types of ischaemic stroke. However, evidence from direct pathological studies is limited because lacunar infarction has a low case fatality, autopsy rates are declining, and informative pathological studies are expensive, technically demanding and time-consuming.

Informative imaging studies are also scarce because of the difficulties in imaging small arteries. Alternative, less direct methods have therefore been used to study the pathology of lacunar infarction. These have included observational studies comparing the risk factor profiles and prognosis of patients with lacunar versus non-lacunar infarction, since differences might suggest distinct arterial pathologies. Systematic review of studies comparing risk factor profiles in lacunar versus non-lacunar infarction found an excess of atrial fibrillation and severe carotid stenosis among non-lacunar infarction

patients, but no clear difference in the frequency of any other risk factors, including hypertension and diabetes.

Aim of the study

To study

*The clinical profile,

*Patterns of vascular involvement.

*Possible etiologies,

*Risk factors identified during the first episode of stroke.

*Risk factors persistent /corrected in the second or subsequent stroke episodes.

*Effects of risk factor treatment on stroke free interval and the occurrence of recurrent stroke

Review of literature

Incidences of recurrent stroke are reported by prospective and retrospective studies as hospital based and community based. Stroke during its first occurrence and recurrence are analyzed on the basis of vascular territory, clinico pathological types used as in Oxfordshire community based study, Toast classification for the risk factors.

Graeme J. Hankey,etal's[1] community-based study aimed to determine the absolute and relative risks of a first recurrent stroke over the first 5 years after a first-ever stroke and the predictors of such recurrence in a population-based series of people with first-ever stroke in Perth, Western Australia from 1989. All people with a suspected acute stroke or transient ischemic attack of the brain who were resident in a geographically defined region of Perth, with a population of 138 708 people, were registered prospectively and assessed. Patients were followed up prospectively at 4 months, 12 months, and 5 years after the index event. Three hundred seventy patients with a first-ever stroke were registered, of whom 351 survived. Data were available for 98% of the

cohort at 5 years, by which time 199 patients (58%) had died and 52 (15%) had experienced a recurrent stroke, 12 (23%) of which were fatal within 28 days. The 5-year cumulative risk of first recurrent stroke was 22.5% (95% confidence limits [CL], 16.8%, 28.1%). The risk of recurrent stroke was 8.8%- greatest in the first 6 months after stroke. (95% CL, 5.4%, 12.1%). After adjustment for age and sex, the prognostic factors for recurrent stroke were advanced, but not extreme, age (75 to 84 years) (hazard ratio [HR], 2.6; 95% CL, 1.1, 6.2), hemorrhagic index stroke (HR, 2.1; 95% CL, 0.98, 4.4), and diabetes mellitus (HR, 2.1; 95% CL, 0.95, 4.4).Approximately 1 in 6 survivors (15%) of a first-ever stroke experience a recurrent stroke over the next 5 years, of which 25% are fatal within 28 days. The pathological subtype of the recurrent stroke is the same as that of the index stroke in 88% of cases. The predictors of first recurrent stroke in this study were advanced age, hemorrhagic index stroke, and diabetes mellitus, but numbers of recurrent events were modest. Because the risk of recurrent stroke is highest (8.8%) in the first 6 months after stroke, strategies for secondary prevention should be initiated as soon as possible after the index event.

Jung B et al [5] did a community-based epidemiologic study. All patients

enrolled as acute ischemic stroke patients from Jan. 1998 to Dec. 2000 analyzed to identify the factors responsible for recurrent ischemic stroke. Among 599 patients with ischemic stroke, 43 patients (7.2%) were had recurrent stroke (27 men and 16 women; mean age=66.3 years). Hypertension and hyperlipidemia were the risk factors which were statistically significant in inducing recurrent ischemic stroke. According to the TOAST classification, cardio embolism was more prevalent in recurrent ischemic stroke.

Jean-Louis Mas [2] et al studied the risks of recurrent cerebrovascular events associated with patent foramen ovale and atrial septal aneurysm . A total of 581 patients (age, 18 to 55 years) who had had an ischemic stroke of unknown origin within the preceding three months were consecutively enrolled at 30 neurology centers. All patients received aspirin (300 mg per day) for secondary prevention. After four years, the risk of recurrent stroke was 2.3 percent (95 percent confidence interval, 0.3 to 4.3 percent) among the patients with patent foramen ovale alone, 15.2 percent (95 percent confidence interval, 1.8 to 28.6 percent) among the patients with both patent foramen ovale and atrial septal aneurysm, and 4.2 percent (95 percent confidence

interval, 1.8 to 6.6 percent) among the patients with neither of these cardiac abnormalities. There were no recurrences among the patients with an atrial septal aneurysm alone. The presence of both cardiac abnormalities was a significant predictor of an increased risk of recurrent stroke (hazard ratio for the comparison with the absence of these abnormalities, 4.17; 95 percent confidence interval, 1.47 to 11.84), whereas isolated patent foramen ovale, whether small or large, was not

Andy H.et al [3] reported Of the 678 patients in the cohort, 124 (18.3%) experienced repeated episodes of ischaemic stroke. Rural residence and carotid endarterectomy procedure were positively associated with the recurrence frequency, the adjusted incidence rate ratio being 1.66 (95% CI: 1.17–2.36) and 3.96 (95% CI: 2.30–6.82), respectively. Rural patients contributed to 18% of the patients in the cohort yet they accounted for 27% of those sustaining repeated episodes of stroke. Readmissions were also related to the presence of diabetes at the index episode.

Goldstein et al [4] identified all patients admitted to Duke University Hospital or the Durham Veterans Administration Medical Center during 1 year having two documented ischemic strokes within 90 days (n=12 of 273).

Twelve randomly selected patients matched for age, sex, and race but having only a single stroke served as controls. There were no significant differences between the groups with respect to a variety of factors including the presence of hypertension, diabetes, a history of transient ischemic attack, a history of stroke, cerebral site of the index stroke, and subtype of the index stroke. A potential cardioembolic source was more frequently identified in the patients with early recurrent stroke (seven of the 12 case-control pairs were discordant for a potential cardioembolic source.

Dong-wha kang et al [7] in a retrospective study reports that Prior observations have shown that early recurrent ischemic lesions (ERILs) on diffusion-weighted imaging occur frequently within the first week after an index stroke. They included 133 patients who experienced an acute ischemic stroke and who underwent initial diffusion-weighted imaging within 24 hours and subsequent diffusion-weighted imaging within 7 days after onset, and whose stroke subtype was Intra cranial large artery atherosclerosis(IC-LAA), extra cranial LAA (EC-LAA), or cardio embolism (CE). Early recurrent ischemic lesions were defined as new ischemic lesions on follow-up diffusion-weighted imaging, separate from the index stroke lesion. Early

recurrent ischemic lesions were observed in the following proportions: 50.9% (28/55) in the IC-LAA group, 47.4% (9/19) in the EC-LAA group, and 44.1% (26/59) in the CE group. Early recurrent ischemic lesions in the IC-LAA group had the following characteristics: (1) they occurred mostly (27 [96.4%] of 28) in the pial area of the same vascular territory as the index stroke; (2) they were more frequently observed in a higher grade of stenosis than in milder stenosis (P<.001), whereas ERILs in the EC-LAA group were not related to the degree of stenosis; (3) they were not associated with subsequent recanalization, whereas ERILs in the CE group were mostly associated with subsequent recanalization (P<.001); and (4) they were more closely associated with clinical recurrence than in the EC-LAA or CE group (P=.02). They conclude that Early recurrent ischemic lesions in the IC-LAA group are relatively frequent and have different patterns than in the EC-LAA or CE group.

Secondary prevention of recurrent stroke by treating the modifiable risk factors have been done in many landmark trials. The prevention of stroke, with its attendant costs, both financial and personal, is the goal of most physicians, but there is good evidence that modification of risk factors

will reduce stroke risk. We'll look at the evidence for the following interventions: treatment of hyperlipidemia, smoking cessation, antiplatelet therapy, treatment of hypertension and anticoagulation for atrial fibrillation.

Aggressive treatment of dyslipidemia decrease the risk of stroke.

This issue has been looked at indirectly in multiple placebo-controlled trials, as a pre-specified secondary end point. Perhaps the best place to demonstrate this is to look at the MRC/BHF study, commonly known as the Heart Protection Study. This is the largest trial ever done on lipid lowering. It included 20,536 people aged 40 to 80 with coronary disease, other occlusive arterial disease or diabetes with a non fasting cholesterol >3.5 mm/l. There were 6,793 subjects with a starting LDL < 3mm/l. They were randomized to 40 mg of simvastatin or a matching placebo. Follow up was for an average of 5 years. 4.3% of the simvastatin group vs. 5.7% of the placebo group suffered a stroke. (RR 75%, RRR 25%, ARR 1.4% NNT 71). This small but consistent effect is seen in multiple trials. There were no excess hemorrhagic strokes in the treatment arm.

Smoking increases the risk of stroke.Clearly we do not have the best Level 1 evidence here as no randomized controlled trials have been done on

this subject. In issues of harm, RCTs are impossible to do, as it is ethically impossible to randomize people to a smoking arm! So we have to look at the next best evidence, a prospective cohort trial, which systematically follows a large group of healthy people until they get ill with the disease of interest, and then tries to elucidate the risk factors for that outcome.

The Framingham Study [19] began soon after WWII, is still ongoing, and is the longest running prospective study of this type. In 1988, it reported on cigarette smoking as a risk factor for stroke. It looked at 4,255 men and women, 36 to 68 years old and free of cerebrovascular disease. During a 26-year follow up 459 strokes occurred. Multivariate analysis using Cox proportional hazard modeling, demonstrated cigarette smoking as an independent risk factor for all strokes in general, and thrombotic strokes in particular. The risk of stroke increased as the number of cigarettes smoked increased. The RR was double in heavy smokers (> 40 cigarettes/ day) compared to light smokers (< 10 cigarettes/day). Lapsed smokers retained their increased risk for the first 2 years, which then gradually decreased over the next 3 years. By 5 years the risk dropped to the level of non-smokers. Regardless of smoking status or sex, hypertension doubled the risk of stroke.

In 1989 a case controlled study[20] looked at 621 patients with stroke and 573 controls without stroke. The authors estimated an increased relative risk of 1.5 for every 10 cigarettes consumed daily, both in men and women.

The use of antiplatelet medications in the secondary prevention of stroke has long been established. Various drugs and combinations of drugs have been studied over the last 20 years. We will look at the evidence for ASA, clopidogrel, and ASA plus dipyridamole.

Acetyl salicylic acid is the best studied, cheapest, and most widely used antiplatelet medication. In 1994 the Antiplatelet Trialists' Collaboration published a meta-analysis of randomized trials[21] of prolonged antiplatelet therapy for prevention of stroke (along with various other endpoints). This meta-analysis looked at trials published till 1990, the vast majority of the patients having taken ASA. Amongst 10,000 patients with a past history of stroke or TIA the net event rate for vascular events was estimated at 18% with antiplatelet therapy vs 22% in the controls. (RR 82%, RRR 18%, ARR 4%, NNT 25).

Ticlopidine was the first antiplatelet drug demonstrated to be clearly better than ASA, however it is not commonly used due to a poor side effect profile.

The second drug in this class to be released was clopidogrel, along with the results of the CAPRIE trial.

The CAPRIE Trial[22] was a randomized, double blinded, international trial designed to assess the relative efficacy of clopidogrel (75 mg. once daily) and aspirin (325 mg. once daily), in reducing the risk of a composite outcome cluster of ischemic stroke, myocardial infarction, or vascular death. The population studied comprised subgroups of patients with atherosclerotic vascular disease manifested as, either recent ischemic stroke, recent myocardial infarction, or symptomatic peripheral arterial disease. 19,185 patients were followed for 1 to 3 years. The primary study end point was a composite of ischemic stroke, MI or vascular death. Overall, in all 3 subgroups, there was an annual 5.32% event rate in the clopidogrel group vs 5.83% in the ASA group. (RR 91.3%, RRR 8.7%, ARR 0.51%, NNT 196/per year, p=0.043).

This is not an impressive result and required a huge study to demonstrate it. In the sub group of interest to us, the 6411 patients with a stroke as the qualifying event to enter the trial, clopidogrel did not demonstrate a significant reduction in the composite endpoint. (RRR 7.3% p=0.26). (An

argument can be made that this was just type 2 error and we just need a larger study to demonstrate a significant difference - but this was already a huge study). Also remember this data is for a composite end point whilst we are most interested here in secondary stroke prevention. So we can conclude that clopidogrel has not been demonstrated to be superior to ASA in the secondary prevention of stroke. Further analysis of this trial supports the view that clopidogrel is clearly superior to ASA in the prevention of MI in the CAPRIE patient population. (RRR 16.6% NNT 119)

By the late 1980's dipyridamole and the combination with ASA was felt to be no better than ASA alone. However, in 1987 ESPS-1 using a combination of ASA 330 mg. plus dipyridamole TID for 2 years in patients with prior ischemic stroke or TIA, showed a RRR of 38% for subsequent stroke. This was far higher than expected from previous studies on ASA alone. There were a lot of questions about the dosing of ASA and the conflicting data of ESPS-1 vs previous trials, so a larger 2x2 factorial design study, ESPS-2[8] was undertaken in 1989 and published in 1996. Placebo was compared to ASA 25 mg. BID, dipyridamole 200 mg. extended release, and the combination of ASA plus dipyridamole. Patients with a prior TIA or

ischemic CVA were enrolled and followed for 2 years in this international multicenter randomized double blinded trial done in Europe.

The results were impressive. 15.78% of the placebo group, 13.21% of the dipyridamole group, 12.93% of the ASA group and 9.95% of the combination group suffered a recurrent stroke. There was no statistical difference between the 2 active treatment groups and with a RRR of 18%, the low dose ASA group was in line with previous trials on ASA. The surprise was the additive effect seen in the combination group. (RR 63%, RRR 37%, ARR 5.83%, $p<0.001$, NNT 17 over 2 years). There was no difference in the death rate in the 4 groups and no excess of MI in the combination group.

From the evidence it is clear the first choice in secondary prevention should be a combination of low dose ASA plus extended release dipyridamole. It is superior to ASA or clopidogrel alone. The combination of ASA and clopidogrel. There is good evidence to use it for ischemic heart disease but the evidence is lacking for secondary prevention of stroke. This is an area of active research and results of several ongoing trials are eagerly awaited.

Hypertension is a major risk factor for stroke and the treatment of hypertension is a powerful means for primary prevention of stroke.

Numerous randomized placebo controlled trials, using primarily diuretics and beta blockers, established this by the 1970's.

Concern about cerebral perfusion in patients with known cerebrovascular disease and especially those with significant carotid disease, meant extrapolation of primary prevention data regarding antihypertensive treatment was resisted till well into the 1990's.

There is the evidence that treatment of hypertension will reduce the risk of stroke in patients who have already suffered a stroke or TIA. This can be reviewed most efficiently by looking at a recent systematic review of the topic published in the Journal STROKE in November 2003. The authors, through an exhaustive search of the world medical literature, identified 7 placebo controlled trials that assessed the effect of lowering blood pressure in patients with prior stoke or TIA. They used meta-analytic techniques to combine these results and came to several not unexpected conclusions. The authors reported the results as odds ratios . The outcome, recurrent stroke, occurred in 11.46% of the placebo group, and 8.86% of the treatment group. (RR77%, RRR23%, ARR2.6%, NNT 38, p=0.005). Interestingly these results were heterogeneous depending on the agent used, but please use caution

interpreting the results, as the numbers are small in each drug class except diuretics.

Overall diuretics decreased the risk of recurrent stroke, ACE-I reduced the risk of MI and the combination of both drugs reduced both. Four of the seven trials used fixed drug combinations and enrolled both hypertensive and non hypertensive patients, bringing up a lively debate on whether the effects seen are related to the drugs used, or the blood pressure drops seen, in the treatment arms. If the effects seen were due to the blood pressure drop, this brings in to play the question of the definitions of hypertension and target blood pressures.

Atrial fibrillation is a potent risk factor for ischemic stroke. This dysrhythmia affects 2-5% of the general population over the age of 60, but is found in 15% of all stroke patients. The use of anticoagulation with warfarin is now well established as the preferred method for primary prevention of stroke in this patient population, as long as the patient is not considered low risk. (Low risk patients have no history of previous stroke or TIA, no treated or untreated hypertension, no diabetes, and no symptomatic coronary artery

disease.)[17] In low risk patients there is no substantive advantage for anticoagulation over antiplatelet agents.

Secondary prevention for a patient who has already suffered a stroke or a TIA associated with atrial fibrillation- This was addressed in 1995 by a Cochrane Review. This review looked at the world literature in a systematic fashion, and performed a meta-analysis on the results. It combined the results of the EAFT from 1993 and VA-SPINAF from 1992. Between the 2 trials 485 patients were included. Anticoagulation reduced the risk of recurrent stroke by nearly 2/3 and the risk of all vascular events over 1/3. (RR 39.5%, RRR 60.5%, $p<0.0001$, ARR 13.7%, NNT 7 for recurrent stroke).

In progress trial 6105 patients with stroke or TIA within 5 previous years were randomized to perindopril+indapamide or placebo. At the end of 4 years they reported a reduction in recurrent stroke of 28% and total major vascular events by 26% inpatients with or without hypertension. Combination therapy with perindopril plus indapamide reduced recurrent stroke by 43% perindopril alone had no significant impact.

WARSS[15-] 2206 patients with a non cardio embolic ischemic stroke were randomized to warfarn (INR 1.4-2.8)or asprin(325mg) .At the end of

2years there was no difference between groups with respect to the primary endpoint (warfarn 17.8% VS asprin 16%) or the rate of major hemorrhage.

In a similar multicentric perspective observational study in setting of primary cause throughout India Sabash Kaul[13] summarized the findings. During 12 months perindopril based treatment it was found that incidence of recurrent stroke was similar to that of progress.

SPARCL [12] investigators assigned 4731 patients who had a stroke or TIA within 1-6 months before study entry had LDL level 100-190 and had no known coronary artery disease to double blind treatment with 80 gm atorvostatin per day or placebo .During 4-9 years absolute reduction in risk of fatal / nonfatal stroke was2.2% & 3.5% reduction in cardiovascular events .There was a small increase in incidence of haemorrhage stroke.

Graeme[30]Quotes that elevation of plasma homocysteine is associated with laboratory evidence of atherogenesis and thombosis and epidemiological evidence of an increased risk of ischemic stroke, independent of other vascular risk factors. The vitamins in stroke prevention trial and the vitamins to prevent stroke trial show insufficient evidence to recommend routine screening and treatment with folic acid B12 and B6.

Materials and methods

This study was conducted during January 2006 to December 2007 at Madras institute of neurology, Government General Hospital, Chennai.

Patients with clinical features suggestive of second or subsequent strokes were taken up for study. All were subjected to CT/MRI scan of brain.

Inclusion criteria

1. All the patients with clinical features suggestive of second or subsequent stroke.
2. Imaging showing ischemic infarcts in the brain

Exclusion criteria

1. First ever episode of stroke
2. Evolving stroke.
3. Imaging showing evidence of hemorrhage.
4. Imaging showing evidence of venous infarct.

Patients' details regarding age, sex, and family history, risk factors like hypertension, diabetes mellitus, hypercholesterolemia, valvular heart disease,

atrial fibrillation, trauma, smoking, and substance abuse were recorded. The onset and details of the symptoms and clinical signs were noted during each stroke episode from the patient or close relative and the old records. All patients had detailed neurological examination.

All patients underwent a basic investigation protocol that included complete blood counts , erythrocyte sedimentation rate, blood glucose, urea ,creatinine, electrolytes, lipid profile (triglycerides, total cholesterol, and fractions) CT brain, chest x-ray, electrocardiogram; transthoracic echocardiogram.

MRI brain with MRA and DWI, B-mode carotid ultrasonography, carotid and vertebral Doppler study had been done wherever indicated.

Other laboratory tests such as homocysteine, fibrinogen, prothrombin time , partial activated thromboplastin time, antinuclear antibodies, anticardiolipin antibody, lupus anticoagulant auto antibodies (anti-SM, anti-SSA, and anti-RNA), were done in selected patients where clinical features indicated their need

Specific studies for the detection of natural anticoagulant deficiency, such as measurement of protein C, protein S, and antithrombin III, were carried out for patients with an undetermined diagnosis and when personal or

family history indicated a prothrombotic disorder. Investigations done during previous stoke episodes were also recorded.

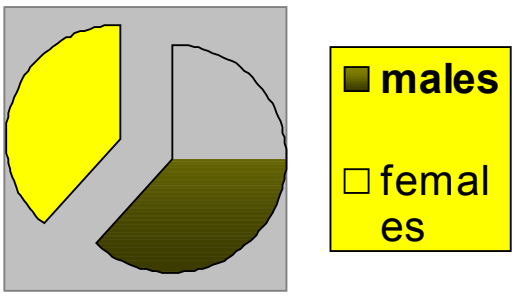
Observation and Results

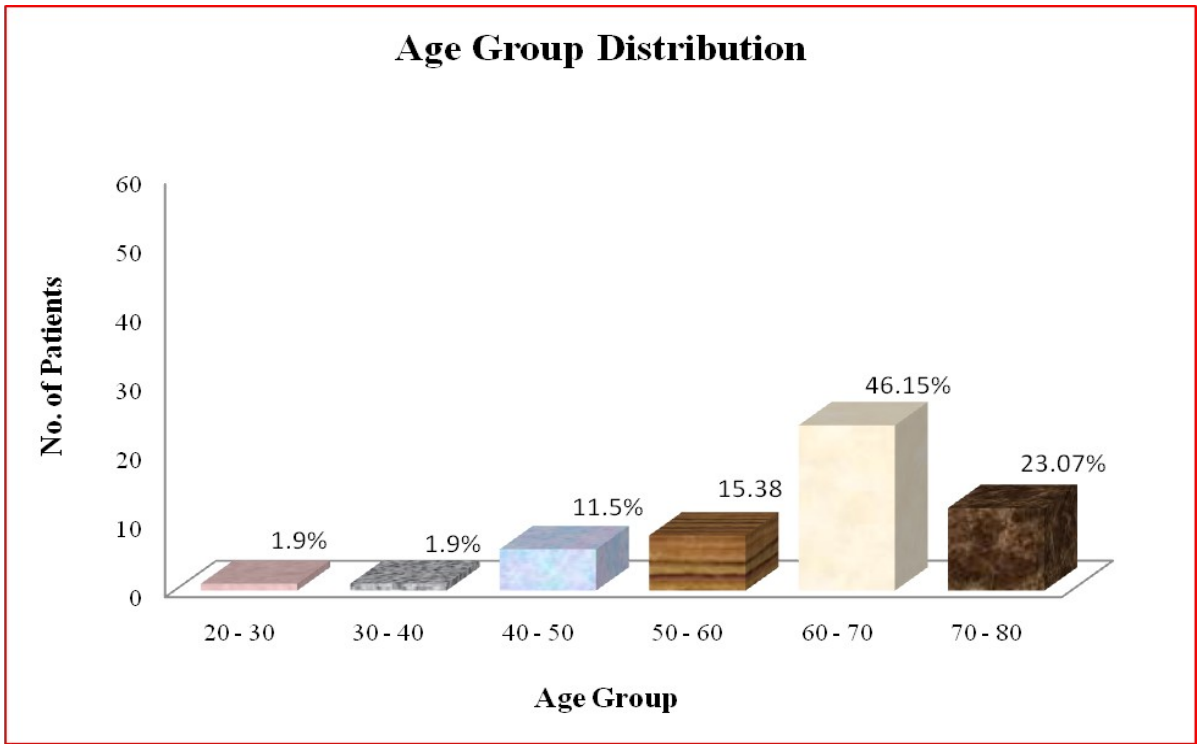
A total of 52 patients admitted in Government General Hospital between January 2005 and December 2006 with clinical features and neuroimaging suggestive of second or subsequent stroke were included in the study.

Sex Distribution

(n=52)

(Males: 61.54%, Females: 38.46%)





Age Distribution

Table-1

(n:52)

Age group	Number of patients	Percentage
20-30	1	1.9
30-40	1	1.9
40-50	6	11.5
50-60	8	15.38
60-70	24	46.15
70-80	12	23.07

Mortality in recurrent stroke

Table-2

(n:52)

Death	No of patients	Percentage
Within one month	2	4
Within one year	4	8
At the end of two years	7	14

Incidence of stroke recurrence

Table-3

Period of occurrence	No of patients (n=52)	**percentage**
First month	**1**	**2**
First 6 months	**6**	**12**
Within 1 One year	**8**	**16**
End of 2 years	**13**	**26**
3rd or subsequent	**39**	**75**

Vascular territory involved in Ischemic strokes

Table-4

Vascular territory involved	First stroke		Subsequent strokes	
	Number of patients	percentage	Number of patients	Percentage
Middle cerebral artery	35	67.31	30	85.71
Posterior cerebral artery	5	9.61	1	20
Anterior cerebral artery	4	7.7	0	0
Verebrobasilar artery	6	11.5	6	33.33
Multiple artery	2	3.84	0	0

(Only ischemic strokes were included in this study)

Risk factors identified during first & subsequent strokes

Table-5

Risk factors	First stroke		Subsequent stroke	
atherosclerotic	**Number Of patients**	**percentage**	**No of patients**	percentage
Hypertention	**32**	**61.54**	8	15.38
Diabetes mellitus	**16**	**30.77**	2	3.84
Dyslipidemia	**12**	**23.08**	2	3.84
Smoking	**30**	**57.69**	4	7.7
Alcoholism	20	38.46	4	7.7

More than 3 out of the following 5 risk factors namely hypertension diabetes, dyslipidemia, smoking and alcoholism was present in 40 cases, (76.92%) as persistent causes, 2 out of 5 in 12 (23.08%).

Non atherosclerotic risk factors

Table-6

Risk factors	Number of patients	**Percentage**
Valvular heart disease	**8**	15.38
Ischemic heart disease	**10**	19.23
Patent foramen ovale+atrial septal aneurysm	**1**	1.92
Aortoareritis	1	1.92

Among the valvular heart disease 6 out of 8 were rheumatic heart disease- mitral stenosis with atrial fibrillation, one was Aortic stenosis with atrial fibrillation and one was infective endocarditis. All the 10 (19.23%) ischemic heart disease patients were in congestive heart failure during the recurrent stroke episode.

Patent foramen ovale with atrial septum aneurysm was detected during the first recurrent stroke. The aortic arteritis patient was on irregular therapy – steroids. The first recurrence occurred during drug withdrawal.

Treatment and its effect on stoke free interval & recurrences

Table-7

Treatment & number of cases	Stroke free interval	**Recurrences**

	(years)	**Number**	**percentage**
Hypertension (32)	**1.5**	15	46.87
Asprin (52)	**2**	10	19.23
Dyslipidemia(12)	2	0	0

All the 32 cases of hypertension were on anti hypertensive and the recurrent stroke occurred during the non compliance. The mean stroke free interval was 1.5 years while on regular treatment recurrence occurred on drug withdrawal.

Ten of the cases had stopped asprin for more than a month accounting for subsequent episode of stroke. The mean stroke free interval was 2 years with good drug compliance.

All the 12 patients with dyslipidemia had elevated LDL and were on 20 mg/ day of atorvostatin. The stroke free interval was 2 years .Recurrence was not reported on 2 cases which had stopped the drug for a period of one month.

Discussion

Only ischemic type of stroke patients was included in this study. 61% of them were males showing a male preponderance. Age group 60-70 had the maximum recurrence stroke (46.15%).This was similar to Jung B et al's [5] report.

The one month mortality rate was 4%, one month stroke recurrence rate 2%, and 1 to 12 month stroke recurrence as 16% in this study. In Carolene jackson's e al's [16] study they were 3.81%,2.11%, and 1.24% respectively. This study shows similar one month mortality rate and more incidences of late recurrence.

Middle cerebral artery was the commonest vascular territory involved(67.31%) in this study as it was in all other recurrent stroke studies .Most of the recurrence was of the same arterial territory -the middle cerebral artery region (85.71%).

Hypertension was found to be the risk factor in majority of cases (61.54%) and diabetes 30.77% in this study. In Jung B et al's [5] study hyperlipidemia was the major associated risk factor. In Perth community study[1] diabetes mellitus was reported in 95% of cases while if is 30.77% in this study.

In this study an attempt was made to analyze the cumulative effect of risk factors on the recurrence of stroke. It was clearly shown that addition of one or more risk factors to the existing one increases the chance of developing recurrence. For example when a hypertensive develops diabetes and dyslipidemia he has more likelihood of developing the next stroke.

This study showed an incidence of 15.38% of valvular heart diseases and 19.23% of ischemic heart disease – showing a marked increase in the incidence of valvular heart disease as a cause recurrent stroke. While Gold stein et al [4] report 30 day recurrence rate of 4.39% with cardio embolic source of other than valvular heart disease.

During the first recurrence we could identify a case of Patent foramen ovale with

atrial septal aneurysm. Masse et al's[32] recommendation that all cryptogenic stokes should be reevaluated proved fruitful.

This study shows stroke free interval of 1.5 years (mean) while on Antihyperensive therapy, 2 years each for patients who were an aspirin and atorvostatin. Progress study [14] reports a reduction in recurrent stroke of 28% with perindopril and indapamide. The event rate was estimated to be 18% with Asprin therapy by antiplatelet trialists' collaboration [21].The reduction in risk of fatal and non fatal stroke was 2.2% with use of statin by Sparcl investigators [12].

Comparison between near similar studies had been made. Other observations made were: Hypertension was the large single contributor and patients on Anti hypertensives had a comparable stroke free interval. Asprin was effective in prolonging the stroke interval. Statin had an added on effect in prolonging stroke free interval.

Biomarkers like high sensitivity C-reactive protein (hs-CRP) and Liporotein associated phospholipase A_2 (L_P-PLA_2) are found to predict recurrent stroke risk. Statins appear to lower hs-CRP levels[33]. A better understanding of these biomarkers may lead to use of prophylactic treatments to reduce risk of people suffering debilitating strokes.

Early recurrent ischemic lesions detected by diffusion weighted image study can predict (1) the presence of higher grade of stenosis in intracranial large artery atherosclerosis subtype of stroke (2) possibility of good recanalization in cardioembolic – ischemic strokes [7]

The recurrent stroke events are relatively small. Confounding factors such as age, sex and co morbid illnesses makes the analysis of prognosis difficult. These limitations highlight the need for pooled multivariate analysis of prognosis among different stroke subtypes using individual patient data from large stroke cohort studies to increase number of patients and outcome events and allow for control of confounding factors.

As a stroke survivor or a caregiver for a stroke survivor, one should know that having a stroke puts the patient at greater risk for getting another stroke[34].

Conclusion

Recurrent strokes account for considerable amount of mortality and morbidity.

Pathological subtype breeds true to the index stroke.

Middle cerebral artery territory is the commonest site involved in recurrent stroke.

Hypertension was the risk factor found in majority of the recurrent episodes.

Presence of three risk factors confers the maximum risk of development of subsequent strokes.

All patients deserve a repeat clinical examination and relevant investigations .This enables to identify new risk factors in cryptogenic strokes and confirm existing and persisting / corrected risk factors.

Aggressive treatment of risk factors will prolong the stroke free interval and prevent the occurrence of recurrent stroke.

Balance of benefits and risks associated with use of various secondary prevention treatments has to be decided on individual basis.

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RECURRENT STROKE - PROFORMA

Name Age: Sex : DOA: DOD: MIN/IP no : Address/Phone no:
Occupation:

Stroke Episodes First Second third fourth

Admission delay
(0-3h,3-6,6-12,12-24,24-48,>48h)

Interval between strokes

Symptoms

1.Headache
2.Nausea/Vomiting
3.Weakness of limbs
4.Numbness face/limbs
5.Mental changes
6.Neck pain
7.Dysphasia
8.Articulation disturbed
9.Impaired vision
10.Diplopia
11.Giddiness/vertigo
12.Dysphagia
13.Imbalance of gait/
in coordination
14.Convulsions-focal /
Generalized
15.Retention of urine
16.Fever
17.Others
18.Altered
consciousness

CLINICAL EXAMINATION:

Obesity Pallor Jaundice Cyanosis Lymph nodes
Skin rash Purpura Xanthelasma
Pulses : carotid vertebral radial dorsalis pedis
Blood pressure :

HMF : conscious drowsy comatose
MMSE :
Lobar functions :

Speech :

Visual acuity visual field
pupils fundus
EOM
Facial palsy
Other cranial nerves :
Bulk:
Tone:
Power : UL : LL :
Reflexes: Abdominal reflex : cremastric :
BJ KJ
TJ AJ
SJ Clonus
Plantar :
Sensory :
Cerebellar :
EPS :
Bladder &bowel:
CVS :
RS :
National Institute of Health Stroke scale(NIHSS)-score:
Modified Rankin Scale-score:

RISK FACTORS-PRESENT STROKE

1.BP on admission: RUL LUL at discharge FH
2.Diabetes mellitus; Blood sugar HbA1c
3.Cardiac diseases;a)IHD/MI b)Atrial fibrillation
c)VHD:Rhematic/Prosthetic
d)Congenital heart disease
4.Dyslipideamia:TC LDL HDL TGL VLDL (mg/dl)
5.Tobacco:
6.Anemia:
7.Homocystinemia(>20/dl)
8.Alcohol:
9.TIA/Previos stroke:
10.Peripheral vascular disease:
11.Obesity:
12.Oral contraceptive use:
13.Drug abuse:
14.Family history of stroke:
15.Trauma:
16.Recent MI(<6weeks):
17.Deep venous thrombosis:
18.Polycythemia:
19.Others(specify….) Veg/Non-veg

INVESTIGATIONS:

Blood : a) Hb : TC : DC : ESR:
Sugar
Urea Creatinine
Total cholesterol Triglyceride
LDL VLDL HDL
b) BT CT PT PTT
Platelet count FDP
Peripheral smea
c) CRP Homocysteine
ANA aCL LAC
p-ANCA c-ANCA
AT-III protein C /
CXR –PA :
ECG :
ECHO :
CT scan : Distribution of hemispheric leision 0.normal
1.cortical
2.subcortical
3.cortical&subcortical
4.brainstem/cerebellum
5.not applicable

Location of leision:
Frontal/parietal/temporal/occipital/basal ganglia /thalamus/sub cortical white matter /cerebellum /midbrain /pons/medulla

MRI : Distribution of hemispheric leis ion
0. Normal
1. Cortical
2. Subcortical
3. Cortical&subcortical
4. brainstem/cerebellum
5. Not applicable

Location of leis ion:
Frontal/parietal/temporal/occipital/basal ganglia
/thalamus/sub cortical white matter/
/cerebellum/midbrain/pons/medulla
DW
Perfusion
MRA
Doppler studies: Carotid & Vertebral Angiography

DIAGNOSIS:

Clinical Radiological

PRESENTATIONS/RISK FACTORS/OUTCOME

Stroke	first	second	third	fourth
Date				
Type of stroke				
Vascular territory				
Subtype of stroke				
Hypertension				
Diabetes				
Smoking				
Alcohol				
Dyslipidemia				
Valvular heart disease				
Coronary artery disease				
Others				
Asprin				
Other drugs				
Drug compliance				
Modified Rankin scale				

A. Type of Stroke:

1.Ischemic 2.Hamorrhage 3.TIA
4. Others 5.Unknown

B.Vascular Territory:

1.Right MCA 2.Left MCA 3.Right ACA
4. Left ACA 5.Right PCA 6.Left PCA 7.Vertebrobasilar

C.Subtype of ischemic stroke:

1a.Large artery extra cranial atherosclerosis
1b.Large artery intracranial atherosclerosis
2. Cardio embolism
3. Small vessel occlusion
4. Stroke of other determined etiology
5. Stroke of other undetermined etiology

Master Chart